ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

TRIAL PROTOCOL

doi:10.1111/add.14242

The safety, effectiveness and cost-effectiveness of cytisine in achieving six-month continuous smoking abstinence in tuberculosis patients—protocol for a double-blind, placebo-controlled randomized trial

Omara Dogar[1], Deepa Barua[2], Melanie Boeckmann[1,3], Helen Elsey[4], Razia Fatima[5], Rhian Gabe[1,6], Rumana Huque[2,7], Ada Keding[1], Amina Khan[8], Daniel Kotz[3,9,10], Eva Kralikova[11,12], James N. Newell[4], Iveta Nohavova[11,12], Steve Parrott[1], Anne Readshaw[1], Lottie Renwick[1], Aziz Sheikh[9], Kamran Siddiqi[1,6] & on behalf of the TB and Tobacco project consortium

University of York, Department of Health Sciences, Faculty of Sciences, York, UK,[1] ARK Foundation, Dhaka, Bangladesh,[2] Institute of General Practice, Addiction Research and Clinical Epidemiology Unit, Medical Faculty of the Heinrich-Heine-University, Düsseldorf, Germany,[3] University of Leeds, Leeds Institute of Health Sciences, Leeds, UK,[4] National Tuberculosis Control Programme (NTP), Islamabad, Pakistan,[5] Hull York Medical School, University of York, Heslington, York, UK,[6] Department of Economics, University of Dhaka, Bangladesh,[7] The Initiative, Islamabad, Pakistan,[8] University of Edinburgh, Usher Institute of Population Health Sciences and Informatics, Edinburgh, UK,[9] Department of Family Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University, the Netherlands,[10] Centre for Tobacco-Dependent of the 3rd Medical Department, Department of Endocrinology and Metabolism, 1st Faculty of Medicine, Charles University and the University Hospital Prague, Czech Republic[11] and Institute of Hygiene and Epidemiology, 1st Faculty of Medicine, Charles University and the University Hospital Prague, Czech Republic[12]

ABSTRACT

Background and aims Tuberculosis (TB) patients who quit smoking have much better disease outcomes than those who continue to smoke. In general populations, behavioural support combined with pharmacotherapy is the most effective strategy in helping people to quit. However, there is no evidence for the effectiveness of this strategy in TB patients who smoke. We will assess the safety, effectiveness and cost-effectiveness of cytisine—a low-cost plant-derived nicotine substitute—for smoking cessation in TB patients compared with placebo, over and above brief behavioural support. **Design** Two-arm, parallel, double-blind, placebo-controlled, multi-centre (30 sites in Bangladesh and Pakistan), individually randomized trial. **Setting** TB treatment centres integrated into public health care systems in Bangladesh and Pakistan. **Participants** Newly diagnosed (in the last 4 weeks) adult pulmonary TB patients who are daily smokers (with or without dual smokeless tobacco use) and are interested in quitting (n = 2388). **Measurements** The primary outcome measure is biochemically verified continuous abstinence from smoking at 6 months post-randomization, assessed using Russell Standard criteria. The secondary outcome measures include continuous abstinence at 12 months, lapses and relapses; clinical TB outcomes; nicotine dependency and withdrawal; and adverse events. **Comments** This is the first smoking cessation trial of cytisine in low- and middle-income countries evaluating both cessation and TB outcomes. If found effective, cytisine could become the most affordable cessation intervention to help TB patients who smoke.

Keywords Bangladesh, cytisine, low- and-middle income countries, Pakistan, placebo-controlled randomized trial, smoking cessation, tobacco cessation, tuberculosis.

Correspondence to: Omara Dogar, University of York, Department of Health Sciences, Faculty of Sciences, Seebohm Rowntree Building, Heslington, York, YO10 5DD, UK. E-mail: omara.dogar@york.ac.uk

Submitted 29 November 2017; initial review completed 24 January 2018; final version accepted 6 April 2018

INTRODUCTION

Tuberculosis (TB) is a widespread and, in many cases, fatal infectious disease. Approximately 85% of TB deaths occur in the low- and middle-income countries (LMICs) in African and the South-East Asian regions [1]. Evidence suggests that smoking increases the risk of developing TB disease [2–4] and leads to poorer outcomes in those TB

patients who continue to smoke [3,5]. Of the 10.4 million incident cases of TB in 2016, an estimated 0.8 million were attributable to smoking [1].

Newly diagnosed TB patients experience high levels of anxiety, including fear of death and worries about infecting others. This provides a 'teachable moment' that health professionals can use to offer smoking cessation advice [6]. 'Teachable moments' are conceptualized as events or sets of circumstances that can lead patients to alter their health behaviour positively [7]. Moreover, the potential health benefits of cessation are greater among TB patients than among other smokers, as most of the tobacco-induced immunological abnormalities in TB patients reverse within 6 weeks of quitting [8]. It therefore makes sense to offer smoking cessation to TB patients who smoke as part of routine care, although this opportunity is rarely taken [9,10].

There is substantial evidence on the effectiveness of behavioural support (BS) and a range of pharmacotherapies available for smoking cessation [11–14]. While these medications, particularly nicotine replacement therapy (NRT) and varenicline, are widely recommended, their costs prohibit their use in LMICs. Cytisine—a plant-derived pharmacotherapy (manufactured as Tabex and Desmoxan)—has recently gained recognition as a safe, efficacious and affordable cessation aid [14,15]. Although cytisine is not licensed in most countries outside eastern Europe [16,17], recent studies [18,19] highlight its potential for use in LMICs [14]. Particularly attractive is its lower cost (US$20–30 for 25 days) in comparison to NRT (US$112–685 for 8–10 weeks) and varenicline (US$474–501 for 12 weeks) [20]. Cytisine was therefore chosen as a suitable medication to trial as part of a project called 'TB and Tobacco'—a European Union (EU)-funded study of tobacco cessation in TB patients in South Asia.

The TB and Tobacco study investigates an innovative approach to improve lung health in LMICs by integrating inexpensive tobacco cessation strategies of proven efficacy into TB programmes. The project has two goals: (i) the effectiveness goal—the TB and Tobacco trial; and (ii) the implementation goal—BS implementation, its process and context evaluation. This protocol focuses on the effectiveness goal.

The primary aim of this trial is to evaluate the effectiveness and cost-effectiveness of cytisine for smoking cessation among TB patients. Secondary aims include assessment of its effectiveness and cost-effectiveness in improving TB outcomes; differential effect by the form of tobacco used; effect moderators: TB severity, socio-economic status (SES), gender and age; adverse effects; nicotine dependency, withdrawals; and process of delivery. An overview of all objectives is listed in Table 1.

METHODS

Design

This is a phase III, double-blind, individually randomized, parallel-group placebo-controlled trial. Participants will receive random allocation in a 1 : 1 ratio to cytisine or matching placebo treatment. Figure 1 illustrates the TB and Tobacco trial flow-chart.

Ethics approval

The trial was granted ethics approval by the Health Sciences Research Governance Committee (HSRGC) at the University of York, UK, by the National Bioethics Committee, Pakistan Medical Research Council (Ref: no. 4–87/16/NBC-200 Part-B/RDC/4197) and by the National Research Ethics Committee, Bangladesh Medical

Table 1 TB and Tobacco trial objectives.

Primary objective
(a) To evaluate the effectiveness and cost-effectiveness of cytisine for smoking cessation among tuberculosis (TB) patients who smoke on a daily basis
Secondary objectives
(b) To assess the effectiveness and cost-effectiveness of cytisine in improving the clinical outcomes of TB patients who smoke tobacco
(c) To assess any differences in the effectiveness by the form of tobacco used (tobacco smoking only versus a combination of smoking and smokeless tobacco)
(d) To assess any differences in the effect across different TB severity groups, high and low socio-economic status (SES), gender and age subgroups
(e) To translate for use in the target population and assess psychometric properties (validity and reliability) of the Mood and Physical Symptoms Scale (MPSS) for the assessment of withdrawal symptoms, and the Strength of Urges to Smoke (SUTS) for the assessment of nicotine dependency
(f) To assess adverse effects of cytisine in the target population
(g) To assess all relevant components of the design and delivery of the smoking cessation programme as part of a process evaluation

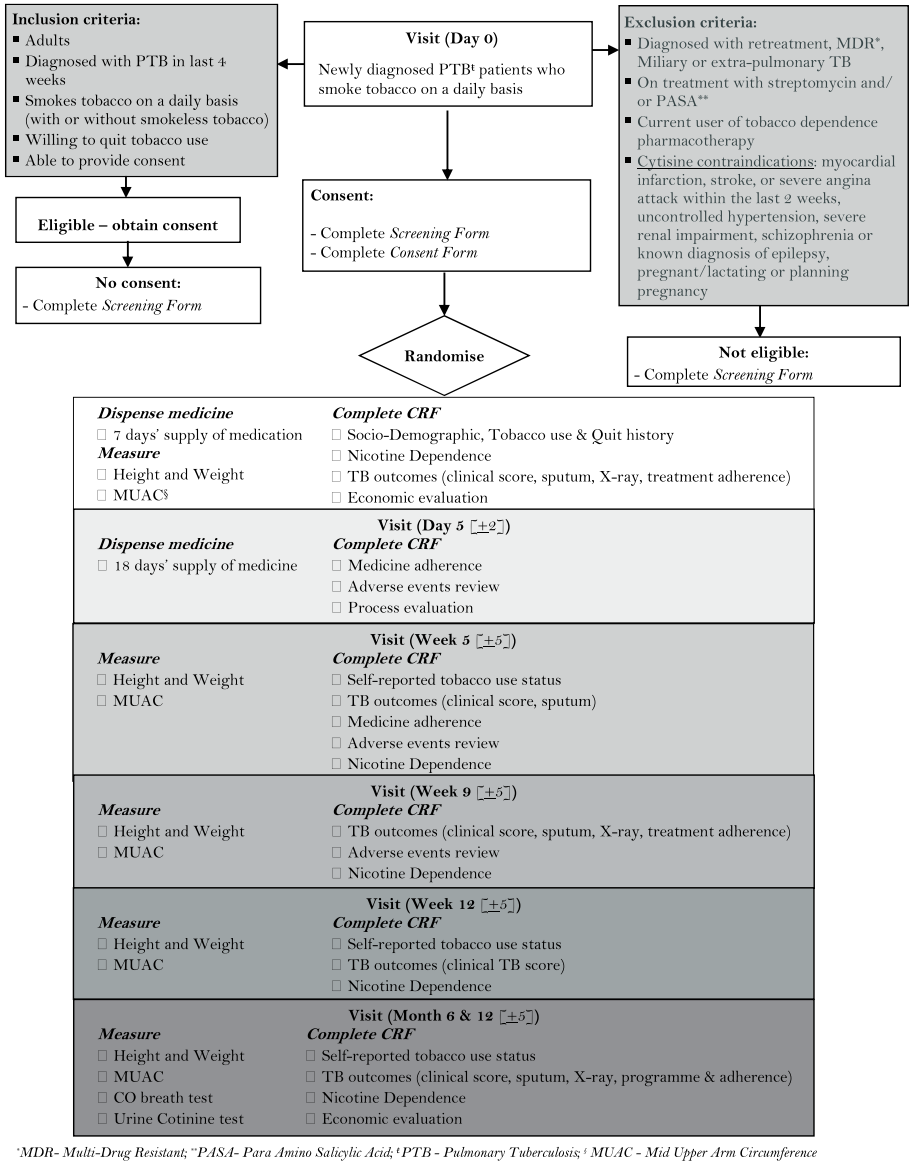

Figure 1 TB and Tobacco trial flow-chart

Research Council (Ref: BMRC/NREC/2016–2019/1475). As cytisine is not licensed for use in either country, approvals were obtained from the Drug Regulatory Authority of Pakistan (1 December 2016) and the Directorate General of Drug Administration in Bangladesh (21 March 2017).

Participants

Participants will be newly diagnosed (within the last 4 weeks) adult pulmonary TB patients who smoke (with or without dual smokeless tobacco use) on a daily basis, wish to quit and are able to provide consent. Table 2 presents participants' eligibility criteria.

Participants will not receive financial incentives except nominal travel costs for any follow-up visits that fall outside routine TB care. The trial will be conducted at 17 sites in Bangladesh and 13 in Pakistan. Sites are designated TB treatment centres run by the respective National TB control Programmes (NTP). Supporting information, Appendix S1 lists the trial sites.

Interventions

All trial participants will receive brief BS for smoking cessation integrated within the more broad advice offered to TB patients to manage their TB and adhere to TB medication. Two face-to-face BS sessions will be delivered at days 0 and 5 (for 10 minutes and 5 minutes, respectively). Further encouragement and support is offered, if needed, at the week 5 visit. BS materials have been translated and adapted to the local context in Bangladesh and Pakistan. The findings relating to the implementation goal of the TB and Tobacco project will inform further adaptation of the BS, to enable

Table 2 Patient eligibility criteria.

Inclusion criteria
(a) Age at least 15 years in Pakistan and 18 years in Bangladesh (definitions of adult TB patients in the two countries)
(b) Able to provide consent
(c) Diagnosed with pulmonary TB (smear-positive or -negative) in the last 4 weeks
(d) Currently smokes tobacco on a daily basis (with or without smokeless tobacco use)
(e) Willing to quit tobacco use
Exclusion criteria
(a) Re-treatment TB, MDR TB, miliary or extra-pulmonary TB
(b) Currently receiving streptomycin (category II anti-TB medication) and/or PASA[a]
(c) Currently using any pharmacotherapy for tobacco dependence
Cytisine contraindications:
(d) Pregnant, lactating or planning to become pregnant
(e) Had myocardial infarction, stroke or an attack of severe angina within the previous 2 weeks
(f) Uncontrolled high blood pressure despite being on medication
(g) Severe renal impairment (requiring dialysis)
(h) Suffering from schizophrenia or known to be diagnosed with epilepsy

TB = tuberculosis; PASA = para amino salicylic acid; MDR = multi-drug-resistant. [a]Using cytisine with anti-TB medicines (PASA, streptomycin) reduces stimulant action of cytisine [39].

scale-up and sustainable delivery within National TB Programmes (see Supporting information, Appendix S2 and Appendix S3 for details on BS).

Randomized patients will receive either cytisine (as Desmoxan) (active arm) or matching placebo (control arm) in their Investigational Medicinal Product (IMP), which is manufactured as 1.5 mg hard capsules for oral administration, with a shelf-life of 2 years. Patients receive 7 days' IMP on the day of enrolment and are expected to return on the fifth day (±2 days), coinciding with their quit date, when they are dispensed another 18 days' supply by the study researcher.

Cytisine

Cytisine, a partial agonist of nicotinic acetylcholine receptors, is pharmacologically similar to varenicline (Chantix). With a half-life of 4.8 hours, cytisine is eliminated rapidly from the body [20]. The standard regimen is a 25-day course, reducing gradually from six capsules a day to one capsule on the last day by the end of the treatment period, with a quit date set for day 5 [15]. Table 3 presents the dosing schedule for the cytisine.

Placebo

Patients in the control arm will receive the placebo in exactly the same manner as cytisine. A checking exercise was carried out using paired samples of capsules to ensure that placebo pills were unrecognizable. Blinded York Trials Unit staff could not distinguish between placebo and active pills based on their appearance, smell or taste.

Outcomes

Patients will have assessments on days 0 (baseline) and 5, weeks 5, 9 and 12 and months 6 and 12. These timepoints, except day 5 and month 12, were chosen to correspond with routine TB care visits. The day 5 visit is to

Table 3 Dosing schedule of cytisine and packing details.

Day of treatment	*Intake interval (1–6 capsules daily during a period of 12 waking hours)*	*Total daily capsules (number included in each packet)*
Days 1–3	1 capsule every 2 hours	6 capsules daily (6 × 3 = 18 capsules per packet)
Days 4–7	1 capsule every 2.5 hours	5 capsules daily (5 × 4 = 20 capsules per packet)
Days 8–12	1 capsule every 2.5 hours	5 capsules daily (5 × 5 = 25 capsules per packet)
Days 13–16	1 capsule every 3 hours	4 capsules daily (4 × 4 = 16 capsules per packet)
Days 17–20	1 capsule every 4 hours	3 capsules daily (3 × 4 = 12 capsules per packet)
Days 21–24	1 capsule every 6 hours	2 capsules daily (2 × 4 = 8 capsules per packet)
Day 25	1 capsule on the last day	1 capsule on the last day

monitor for any adverse drug reaction and the month 12 visit is to assess longer-term smoking cessation and any TB relapses. Table 4 provides the schedule for trial participants from initial eligibility screening, dispensing of IMP and the data collection/assessments.

Primary outcome measure

The primary outcome is biochemically verified continuous smoking abstinence at 6 months post-randomization, as per Russell Standard [21]; self-report of not using more than five cigarettes/bidis/water pipe sessions/chewing tobacco products from the quit date (5 ± 2 days) supported by a negative exhaled carbon monoxide [CO < 10 parts per million (p.p.m.)] test at 6 months, using a Micro MC02 CO Monitor (CareFusion UK Ltd, Wokingham, UK). In concomitant smokeless tobacco users, instead of CO, a cotinine dipstick test (OneStep Urine Test Strip, sensitivity 200 ng/ml, supplied by Home Health UK, Bushey, UK) will be used for biochemical verification of abstinence. An elevated CO or cotinine level will always take precedence over the patient's self-reported abstinence. In the analysis, patients will be considered smokers if their smoking status could not be determined.

Although smoking status is assessed at both 6 and at 12 months' time-points, in the interest of better retention rates primary outcome is measured at 6 months.

Secondary outcome measures

Abstinence, lapses and relapses. Abstinence, lapses and relapses comprise: continuous abstinence at 12 months (same definition as for primary outcome at 6 months); point abstinence, defined as a self-report of not using tobacco in the previous 7 days at weeks 5 and 12 and at months 6 and 12 (abstinence is verified biochemically at months 6 and 12 only). In addition, early-lapse, late-lapse, early-relapse and late-relapse will be assessed according to the definitions presented in Table 5.

TB outcomes. Assessment for the impact of smoking cessation on TB outcomes includes clinical TB score [22–24]; sputum conversion results; chest X-ray grading (normal, minimal, moderately advanced or far advanced TB) [25]; adherence to TB treatment; and standard TB treatment outcomes (success, failure, default, relapse or death). The researchers will assess signs and symptoms for TB score (supported by the clinical team), while routine reporting on TB cards/registers maintained by the TB programme will provide the remaining TB outcomes. Table 6 presents the definitions of the TB outcomes.

Nicotine dependency. Assessment of nicotine dependency includes translated versions of the Mood and Physical Symptoms Scale (MPSS) [27], the Strength of Urges To

Table 4 Schedule of enrolment and follow-up assessments for TB and Tobacco trial.

	Study period						
Assessment			*Week 5*	*Week 9*	*Week 12*	*Month 6*	*Month 12*
Time-point	*Day 0*	*Day 5*	*(day 35)*	*(day 63)*	*(day 84)*	*(week 25)*	*(week 52)*
Allowed variation in days		−/+2 days	−/+5 days				
Eligibility screen	x						
Informed consent	x						
Randomization	x						
Tobacco use (self-reported)	x		x		x	x	x
Socio-demographic history[a]	x						
Tobacco use and quit history[b]	x						
Nicotine dependence[c]	x		x		x	x	x
Economic outcomes	x					x	x
Process outcomes	x	x					
Tobacco use (biochemical measures)						x	x
Study medication dispensing	x (for 7 days)	x (for 18 days)					
Medication adherence		x	x				
Adverse events review (checklist)		x	x	x			
Clinical TB score	x		x	x	x	x	x
TB sputum conversion	x		x	x		x	x
TB chest X-ray grading	x			x		x	x
TB treatment adherence	x			x		x	
TB treatment outcomes						x	x

TB = tuberculosis. [a]Socio-demographic history includes: age, gender, marital status, household assets, education, work status; [b]tobacco use and quit history includes: initiation, duration, type, frequency and quantity of tobacco use, smoking restrictions inside homes, number of quit attempts, last quit attempt and duration of longest quit attempt; [c]nicotine dependence includes: Mood and Physical Symptoms Scale, Strength of Urges To Smoke scale and Heaviness of Tobacco Index.

Table 5 Smoking cessation outcomes: primary and secondary measures.

Outcome	*Definition*
Primary outcome measure: Continuous abstinence (at 6 months)	Self-report of not using more than five cigarettes/bidis/water pipe sessions/chewing tobacco products from the quit date (5 +/− 2 days) to the reporting date, supported by a negative biochemical test at 6 months
Secondary outcome measures: Continuous abstinence (at 12 months)	Self-report of not using more than five cigarettes/bidis/water pipe sessions/chewing tobacco products from the quit date (5 +/− 2 days) to the reporting date, supported by a negative biochemical test at 12 months
Point abstinence	Self-report of not using tobacco in the previous 7 days, assessed at weeks 5 and 12, and at months 6 and 12
Early-lapse	Self-report of tobacco use (even once) after the quit date but having point abstinence at week 5
Late-lapse	Self-report of tobacco use (even once) between weeks 5 and 12 but showing point abstinence at weeks 5 and 12
Early-relapse	Abstinence at week 5 but a self-report of tobacco use by week 12
Late-relapse	Abstinence at weeks 5 and 12 but a self-report of tobacco use by month 6

Table 6 TB outcomes.

TB score	TB score consists of the following clinical signs and symptoms of TB: cough, chest pain, dyspnoea, anaemia, BMI < 18 kg/m^2, MUAC < 220 mm. Each of the six clinical variables contributes 1 point, and BMI and MUAC contribute an extra point if < 16 kg/m^2 and < 200 mm, respectively, hence the maximum score of 8. Assessments for TB score are at day 0, weeks 5, 9 and 12 and months 6 and 12. The TB score will be categorized into four severity classes (I–IV): SC I < 2 points, SC II 2–3 points, SC III 4–7 points and SC IV > 7 points [22]
Sputum conversion	Sputum conversion results obtained at weeks 5 and 9 and at months 6 and 12, from routine TB laboratory testing
Chest X-ray grading	Chest X-rays reports obtained at day 0, week 9 and months 6 and 12 graded according to the National Tuberculosis Association of the USA grades by a senior radiologist will be categorized into four grades as 0 (normal), 1 (mild), 2 (moderate) and 3 (far advanced TB) [40]
Treatment adherence	TB patient's medication logs (for anti-TB medication) consulted from routine TB cards will provide adherence assessments at day 0, week 9 and month 6
Programme outcomes	Programme outcomes, as defined [41] below, recorded from routine TB registers at month 6. Additionally, relapse assessed at month 12 follow-up *Cured:* 'A patient who was initially smear-positive and who was smear negative in the last month of treatment (at month 6) and on at least one previous occasion' *Completed treatment:* 'A patient who completed treatment (at month 6) but did not meet the criteria for cure or treatment failure' *Treatment failure:* 'A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment' *Defaulted:* 'A patient whose treatment was interrupted for 2 consecutive months or more' *Died:* 'A patient who died from any cause during treatment' *Relapsed:* 'A patient who was previously treated for TB, was declared cured or treatment completed at the end of his most recent course of treatment, and is now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by re-infection)'

TB = tuberculosis; BMI = body mass index; MUAC = mid upper arm circumference; SC = severity class.

Smoke (SUTS) scale [26] and the Heaviness of Smoking Index (HSI) [28,29] in Bangla and Urdu.

Adverse events. Table 7 presents definitions of adverse events (AEs), which will be collected up to week 9, and self-reports recorded on the 'AEs review' checklist in the patient case-report form that is compiled from the summary of product characteristics for Desmoxan and previous relevant randomized controlled trials (RCT) [16,19,30,31]. The checklist includes symptoms relating to possible cytisine side effects: nausea, diarrhoea, dry mouth, epigastric pain, headache, insomnia, abnormal dreams, irritability, anxiety, tachycardia and musculoskeletal pain. A clinical review will be required for patients reporting any

Table 7 Definitions of adverse events.

Term	*Definition*
Adverse event (AE)	Any untoward medical occurrence in a patient to whom an IMP has been administered including occurrences that are not necessarily caused by or related to that product
Adverse reaction (AR)	Any untoward and unintended response to an IMP related to any dose administered
Unexpected adverse reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the SPC for that product, patient information leaflet, IB or protocol
Serious adverse event (SAE) or serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening[a] ▪ Requires hospitalization or prolongation of existing hospitalization[b] ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect

[a]The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, [b]hospitalization is defined as an in-patient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Hospitalizations for a pre-existing condition, that has not worsened or for an elective procedure, do not constitute an SAE, for example, a silent myocardial infarction. IMP = Investigational Medicinal Product; SPC = Summary of Product Characteristics; IB = Investigator Brochure.

moderate to severe symptoms, classified using the Common Terminology Criteria for Adverse Events (CTCAE) [32]. A site-designated clinician, trained in study-related AEs, will review and determine the severity and relationship of the event to the study treatment.

The researcher at each site will notify all serious adverse events to the country coordinating office within 24 hours of becoming aware of an event, who will in turn notify the York trial team within (a further) 24 hours. Medically qualified staff at the country coordinating office will confirm 'causality' and 'expectedness' and code these events using the Medical Dictionary for Regulatory Activities (MedDRA) [33].

Adherence. Adherence will be monitored using a questionnaire at day 5 and each subsequent follow-up appointment, as well as by counting empty cells in the blister packets (day 5 and week 5). Dosing schedule cards will be provided to help to maximize adherence.

Process evaluation. A mixed-methods process evaluation will assess reach, dose received, dose delivered and fidelity for trial and BS components; the protocol is submitted separately for publication.

Sample size

The sample size is based on known cessation rates for BS and previously observed group differences using cytisine. The Action for Stopping Smoking In Suspected TB (ASSIST) trial (based on 1955 patients in Pakistan) reported that 41% of regular smokers with presumptive TB sustained biochemically verified smoking cessation at 6 months after random allocation to BS [34]. Previous RCTs of cytisine have shown increases of 6–7% (differences in absolute percentages) for sustained cessation [16,19,30]. To detect an increase of 6% in the 6-month abstinence rate for the addition of cytisine to BS, from 41 to 47% with 80% power, testing at the 5% significance level, requires primary outcome data for a total of 2148 participants (1074 in each arm). The ASSIST trial reported missing primary outcome data on 5.5% of participants. Assuming a more conservative attrition rate of 10% gives a target recruitment of 2388 participants (1194 in each arm).

Randomization

Allocation to the trial arms is by pre-prepared block randomization lists for each country, generated by the trial statistician. IMP packs are labelled sequentially in their randomized order and distributed to trial sites in batches. Once a patient has consented to participate, the researcher at the site calls the country coordinating office to obtain the patient's allocated trial number and confirm the next IMP pack number in the sequence to dispense to the patient.

Blinding

Patients, clinical team and researchers will remain blind to treatment allocation. To ensure double-blinding, IMP packs appear identical and only the code-break envelopes prepared separately for each trial number could ascertain treatment allocation. In an emergency, any request to un-blind must be authorized by a clinician or senior trial staff. Each country coordinating office will be contactable

by in- and out-of-office hours contact numbers; the contacted staff will need to travel to the office in order to access the code-break envelopes and follow the procedure for un-blinding as per manual of operations.

Statistical methods

Analyses will be based on intention-to-treat, analysing participants in the arm to which they were randomized. Significance tests will be two-sided at the 5% level. Baseline characteristics (see Table 4 for details) will be presented descriptively to assess balance between cytisine and placebo arms in terms of: (a) ecological factors at the TB treatment centre level; and (b) individual factors at patient level.

Primary analysis

Missing primary outcome data will be treated as a negative outcome, i.e. continuous smoking [21]. Agreement between self-reported and biochemically verified abstinence will be reported by trial arm. The number and proportion of abstinent patients will be reported by trial arm, and group differences will be illustrated by the risk difference and relative risk with associated 95% confidence intervals (CIs) and *P*-values. Abstinence rates will be compared between the active and the control arms using logistic regression. Trial sites will be included as a random effect using robust standard errors.

Secondary outcomes analysis

The primary analysis will be repeated for the following secondary outcomes: continuous abstinence for 12 months, point abstinence at weeks 5 and 12 and months 6 and 12, as well as early and late lapses and relapses (Table 5). Point abstinence will be plotted over time. TB outcomes of TB score, sputum conversion, X-ray assessment, treatment adherence and programme outcomes, as well as withdrawal and dependency as measured by MPSS and SUTS, will be analysed using appropriate statistical models for continuous or categorical data using all available time-points.

The total number of AEs, the number of patients with any AE and the number of AEs per patient will be reported by trial arm. The number of patients with any AE will be compared by χ^2 test between arms.

Levels of adherence to study treatment will be presented descriptively [means and standard deviations (SDs), as well as grouped as $\geq$ 80% (strong adherence), $<$ 80% but $\geq$ 50% (moderate adherence) and $<$ 50% (poor adherence)]. Compliers will be defined as those having taken any dose of medication on 80% or more of the prescribed days. Patients with missing data at 5 weeks will be assumed to be non-compliant with the trial regimen.

Sensitivity analyses

Sensitivity analyses will include: (i) primary analysis adjusting for baseline level of dependence; (ii) primary analysis adjusting for baseline level of dependence, age, gender, form of tobacco use and any potentially influential baseline variables for which chance imbalances between groups may have been observed; and (iii) an appropriate repeat of the primary analysis that takes treatment adherence into account.

Subgroup analyses

The primary logistic regression analysis will be repeated, including a treatment × subgroup interaction for six subgroups, collected at baseline: (i) tobacco use (smoked only, smoked and smokeless), (ii) gender (male, female), (iii) age ($<$ 40, $\geq$ 40), (iv) TB severity (I–IV), (v) SES (percentile cut-off of a wealth index derived from education/household assets/work status) and (vi) country (Pakistan, Bangladesh). Abstinence rates, risk differences and relative risk for each subgroup will be reported with 95% CIs. *P*-values for the interaction terms will be reported; however, the trial is not powered to detect interactions.

Cost-effectiveness analysis

In order to undertake a full cost-effectiveness analysis (CEA), costs of the interventions and participants' use of wider health care (e.g. doctor visits, hospital attendances, etc.) will be collected for both groups. Basic unit costs collected alongside the trial will then be applied to complete health-care cost profiles. The costs of patients' TB-related care will be included in the service-use questionnaires and costs allocated accordingly. Two outcomes will be used for the CEA; quitters (primary outcome) and quality-adjusted life-years (QALYs), calculated from the EQ-5D-5 L (a measure of health utility) collected during the trial [35]. We will calculate incremental cost-effectiveness ratios (ICER) combining treatment and wider health-care costs with each outcome.

Bootstrapping techniques will be employed and cost-effectiveness planes and cost-effectiveness acceptability curves will be constructed to reflect any uncertainty in the results and threshold. The CEA will demonstrate the value for money of adding cytisine to BS from the perspective of the service provider (the public or voluntary sector). We will also estimate the wider societal cost to patients, with a supporting analysis presenting the costs to patients incurred from out-of-pocket payments, productivity loss and travel costs.

Oversight committees

Trial oversight committees include an Independent Steering Committee (ISC), an independent Data

Monitoring and Ethics Committee (DMEC) and the Trial Management Team (TMG). Only the DMEC will have access to the unblinded comparative data from the trial. The study will be stopped, as guided by the ISC and DMEC, if: (i) new literature indicates findings that can be applied to this question in terms of benefit or side effects. However, early evidence of clear benefit would not be a reason to halt recruitment in the trial because data on TB outcomes would still be useful for the full sample size. (ii) Reporting of AEs indicates that review of the study protocol is required for the study medication.

Dissemination policy

Results will be disseminated to key stakeholders and patients in several ways. These include: open-access peer-reviewed journal articles; presentation at key scientific meetings; posting on the study website; feedback to trial participants; press releases at collaborating universities. We will explore non-academic routes to dissemination, for example through the NTPs in Bangladesh and Pakistan. The findings of the TB and Tobacco trial will be made public (after academic publication), in accordance with the requirements of the funder (EU) and *Addiction* journal. We are committed to share our behavioural support intervention materials and the related training packages at the end of the study. Requests for access to data and code will be reviewed by the study Chief Investigator and confirmed with the sponsor (University of York). The criteria for authorship will be taken from the International Committee of Medical Journal Editors [38].

Trial status

The current HSRGC approved protocol is version 3.0 (24 March 2017). This manuscript is a re-structured and edited version of the current approved protocol, to comply with the CONSORT reporting guidelines. The first patient was recruited into the trial on 06 June 2017 in Pakistan and 22 July 2017 in Bangladesh. Recruitment is anticipated to be complete by the end of May 2018.

DISCUSSION

Our trial is innovative and important in several ways. To our knowledge, this is the only pragmatic RCT investigating the safety, effectiveness and cost-effectiveness of cytisine for smoking cessation in LMICs and in TB patients. It is also, so far, the largest trial of cytisine in the world. Despite an overwhelming case for providing cessation support to TB patients [36], this has generally not been conducted. Lack of evidence on cheap and effective solutions has been a significant barrier. For those living in LMICs it may be considered less expensive to continue smoking than to purchase smoking cessation medications [19]. Cytisine, if proven effective, can offer a cheaper alternative to other cessation aids. Furthermore, because cytisine is a plant-based medication, adherence may be better than with synthetic products. It may fit well with certain cultures blending traditional approaches with western-style medicine.

The current evidence on the effectiveness of smoking cessation interventions, based on quit rates, has had limited success in convincing TB managers to include these in routine TB care. Our trial will test the impact of smoking cessation on TB outcomes—a key strength of this study. This could provide leverage to include cessation within routine TB care. Identifying cost-efficient means to influence TB and tobacco—the two converging epidemics—could benefit policy directions in the area [37].

Our trial is conducted in Pakistan and Bangladesh, where smokeless tobacco use is common. With any efforts towards encouraging people to quit smoking, there are always concerns that people may quit smoking but switch to smokeless tobacco. A unique feature of this study is that it can assess any substitution between smoking and smokeless tobacco.

The study's results will need to be considered in the light of some caveats, including some anticipated risks. Trial participants' adherence with the complicated dose regimen of cytisine could be a potential issue. While we will assess adherence with cytisine using a number of self-reported measures, we are concerned that participating TB patients may find it challenging to take cytisine (with its frequent dosing schedule) along with their TB treatment. Given that ours is an effectiveness trial, any attempts to increase adherence are limited to what is feasible in the real world. It is also important to acknowledge that if BS is not delivered or is not as effective as in previous trials, then cytisine may have lesser (or greater) impact. Secondly, the study is not powered statistically to detect any differences between the two arms for TB outcomes. However, we can provide estimates for future research on TB outcomes by quit status in the cohort. We will also use our data for a future cumulative meta-analysis to ascertain effectiveness of such interventions on TB outcomes.

Lastly, although cytisine has been used in eastern Europe and in New Zealand, it has not been used in a study in South Asia (tropical climate zone), and its stability and pharmacovigilance have not been tested in the temperatures and humidity encountered in this zone. Although we will control the storage conditions of cytisine for the study within the manufacturer's recommended range, there is a need for a pharmacovigilance study of cytisine to establish its stability under different climatic conditions.

A placebo-controlled trial of cytisine raises some questions on the ethics of depriving at least 50% patients of a treatment that has some good evidence of its efficacy. Conversely, all trial participants are offered behaviour support

with specific advice for patients on how to quit, with the leaflet as an additional resource to take home. Besides, in the current scenario, TB patients who smoke have almost no chance of acquiring any smoking cessation medication; in our trial they have at least a 50% chance. Furthermore, the evidence on the efficacy of cytisine is still not completely established.

Retention and dropout is a key issue for all smoking cessation trials. Nonetheless, we will ensure that, where possible, retention remains high. To our advantage, the trial participants will have most of their follow-ups in line with their routine TB treatment visits. However, higher attrition rates are anticipated once TB treatment is completed. We will set up follow-up reminders (text messages or phone calls) and home visits for patients who are unable or unwilling to visit the trial sites.

To summarize, if cytisine is found to be effective, it will be an affordable option for policy makers in LMICs to consider when including smoking cessation in TB programmes.

Clinical trial registration

International Standard Randomized Clinical Trial Number (ISRCTN43811467).

Declaration of interests

K.S. received a research grant from Pfizer (2015–2017) to study the effect of varenicline (a smoking cessation medicine) on waterpipe smoking cessation. E.K. received payment from pharmaceutical companies providing smoking cessation medications for clinical studies, educational and consultation activities.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme, under Grant Agreement No. 680995. Aflofarm Pharma Poland provided cytisine (Desmoxan) and placebo free of cost for the trial; however, they have no role in the trial conduct, its analysis or dissemination of results. We would like to thank Farid Ahmed, Mahboob ul Haq, Salman Sohail, Sonia Raja and the researchers based at the study sites for their work on the trial.

References

1. World Health Organisation. Global Tuberculosis Report 2017. Available at: http://www.who.int/tb/publications/global_report/en/ (accessed 3 March 2018) (Archived at http://www.webcitation.org/6xcF72zRw on 3 February 2018).
2. Bates M. N., Khalakdina A., Pai M., Chang L., Lessa F., Smith K. R. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007; **167**: 335–42.
3. Lin H., Ezzati M., Murray M. Tobacco smoke. Indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLOS Med* 2007; **4**: e20.
4. Slama K., Chiang C., Enarson D., Hassmiller K., Fanning A., Gupta P. *et al*. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis [Review]. *Int J Tuberc Lung Dis* 2007; **11**: 1049–61.
5. Altet-Gomez M., Alcaide J., Godoy P., Romero M., Hernandez del Rey I. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13038 cases. *Int J Tuberc Lung Dis* 2005; **9**: 430–6.
6. Elsey H., Dogar O., Ahluwalia J., Siddiqi K. Predictors of cessation in smokers suspected of TB: secondary analysis of data from a cluster randomized controlled trial. *Drug Alcohol Depend* 2015; **155**: 128–33.
7. Lawson P. J., Flocke S. A. Teachable moments for health behavior change: a concept analysis. *Patient Educ Couns* 2009; **76**: 25–30.
8. Arcavi L., Benowitz N. L. Cigarette smoking and infection. *Arch Intern Med* 2004; **164**: 2206–16.
9. Ng N., Padmawati R., Prabandari Y., Nichter M. Smoking behavior among former tuberculosis patients in Indonesia: intervention is needed. *Int J Tuberc Lung Dis* 2008; **12**: 567–72.
10. Lee A. C. K., Siddiqi K., Khan M. A., Ahmed M., Shams N., Nazir A. Local determinants of tobacco use in Pakistan and the importance of context. *J Smok Cessat* 2010; **5**: 145–50.
11. National Institute for Health and Care Excellence (NICE). Smoking Cessation Services in Primary Care, Pharmacies, Local Authorities and Workplaces, Particularly for Manual Working Groups, Pregnant Women and Hard to Reach Communities, no. 10. February. London: NICE; 2008.
12. Stead L. F., Perera R., Bullen C., Mant D., Hartmann-Boyce J., Cahill K. *et al*. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012; **11**: CD000146.
13. Hughes J. R., Stead L. F., Hartmann-Boyce J., Cahill K., Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014; **1**: CD000031.
14. Cahill K., Lindson-Hawley N., Thomas K. H., Fanshawe T. R., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2016; **4**: CD006103.
15. Cahill K., Stevens S., Perera R., Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013; **5**: CD009329.
16. Walker N., Howe C., Glover M., McRobbie H., Barnes J., Nosa V. *et al*. Cytisine versus nicotine for smoking cessation. *N Engl J Med* 2014; **371**: 2353–62.
17. Walker N., Bullen C., Barnes J., McRobbie H., Tutka P., Raw M. *et al*. Getting cytisine licensed for use world-wide: a call to action. *Addiction* 2016; **111**: 1895–8.
18. Vinnikov D., Brimkulov N., Burjubaeva A. A double-blind, randomised, placebo-controlled trial of cytisine for smoking cessation in medium-dependent workers. *J Smok Cessat* 2008; **3**: 57–62.
19. West R., Zatonski W., Cedzynska M., Lewandowska D., Pazik J., Aveyard P. *et al*. Placebo-controlled trial of cytisine for smoking cessation. *N Engl J Med* 2011; **365**: 1193–200.
20. Prochaska J. J., Das S., Benowitz N. L. Cytisine, the world's oldest smoking cessation aid. *BMJ* 2013; **347**: f5198.
21. West R., Hajek P., Stead L., Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005; **100**: 299–303.
22. Rudolf F., Lemvik G., Abate E., Verkuilen J., Schön T., Gomes V. F. *et al*. TBscore II: refining and validating a simple clinical

score for treatment monitoring of patients with pulmonary tuberculosis. *Scand J Infect Dis* 2013; **45**: 825–36.
23. Janols H., Abate E., Idh J., Senbeto M., Britton S., Alemu S. *et al*. Early treatment response evaluated by a clinical scoring system correlates with the prognosis of pulmonary tuberculosis patients in Ethiopia: a prospective follow-up study. *Scand J Infect Dis* 2012; **44**: 828–34.
24. Wejse C., Gustafson P., Nielsen J., Gomes V. F., Aaby P., Andersen PL *et al*. TBscore: signs and symptoms from tuberculosis patients in a low-resource setting have predictive value and may be used to assess clinical course. *Scand J Infect Dis* 2008; **40**: 111–20.
25. National Tuberculosis Association of the USA. Diagnostic Standards and Classification of Tuberculosis. Smyrna, GA: National Tuberculosis Association of the USA; 1961.
26. Fidler J. A., Shahab L., West R. Strength of urges to smoke as a measure of severity of cigarette dependence: comparison with the Fagerström Test for Nicotine Dependence and its components. *Addiction* 2011; **106**: 631–8.
27. West R., Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004; **177**: 195–9.
28. Borland R., Yong H.-H., O'connor R., Hyland A., Thompson M. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control Four Country study. *Nicotine Tob Res* 2010; **12**: S45–50.
29. Baker T. B., Piper M. E., McCarthy D. E., Bolt D. M., Smith S. S., Kim S.-Y. *et al*. Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. *Nicotine Tob Res* 2007; **9**: S555–70.
30. Hajek P., McRobbie H., Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. *Thorax* 2013; **68**: 1037–42.
31. Cinciripini P. M., Robinson J. D., Karam-Hage M., Minnix J. A., Lam C., Versace F. *et al*. The effects of varenicline and bupropion-SR plus intensive counseling on prolonged abstinence from smoking, depression, negative affect and other symptoms of nicotine withdrawal. *JAMA Psychiatry* 2013; **70**: 522–33.
32. Basch E., Iasonos A., McDonough T., Barz A., Culkin A., Kris M. G. *et al*. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol* 2006; **7**: 903–9.
33. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities (MedDRA). Available at: https://www.meddra.org/ (accessed 2 March 2018) (Archived at http://www.webcitation.org/6xcLkRFYu on 3 February 2018).
34. Siddiqi K., Khan A., Ahmad M., Dogar O., Kanaan M., Newell J. N. *et al*. Action to stop smoking in suspected tuberculosis (ASSIST) in Pakistan: a cluster randomized, controlled trial. *Ann Intern Med* 2013; **158**: 667–75.
35. van Hout B., Janssen M., Feng Y.-S., Kohlmann T., Busschbach J., Golicki D. *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**: 708–15.
36. World Health Organization. *A WHO/The Union Monograph on TB and Tobacco Control*. Geneva: World Heath Organization; 2007.
37. Siddiqi K. Supporting economically disadvantaged tobacco users to help them stop: time to review priorities? *Addiction* 2014; **109**: 1221–2.
38. International Committee of Medical Journal Editors. Available at: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html (accessed 2 March 2018) (Archived at http://www.webcitation.org/6xcPfvmoG on 3 February 2018).
39. TOXNET: Toxicology Data Network. Cytisine (Pharmacokinetics, Interactions). Available at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3560 (accessed 3 March 2018) (Archived at http://www.webcitation.org/6xcHm5qS9 on 3 February 2018).
40. Abate E., Elias D., Getachew A., Alemu S., Diro E., Britton S. *et al*. Effects of albendazole on the clinical outcome and immunological responses in helminth co-infected tuberculosis patients: a double blind randomised clinical trial. *Int J Parasitol* 2015; **45**: 133–40.
41. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: 2013.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix S1 TB and Tobacco trial participating sites.

Appendix S2 Generic behavioural support package.

Appendix S3 Generic health worker guide.

